The Impact of the Transcanal Endoscopic Approach and Mastoid Preservation on Recurrence of Primary Acquired Attic Cholesteatoma

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Short title

Mucosa Preservation in Primary Acquired Attic Cholesteatoma

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Disclosure

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Conflict of Interests

The authors declare no conflict of interest.

Key Words

Cholesteatoma; mucosa preservation; endoscopic ear surgery; outcome; results; recurrence; mastoidectomy; minimal-invasive surgery

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Abstract

Objective: We aim to investigate the factors associated with recurrent disease following surgery for primary acquired attic cholesteatoma. We hypothesize that minimal invasive, mucosal sparing operation techniques have beneficial effects on the outcome in terms of recurrence.

Study Design: Retrospective Study

Setting: Tertiary referral center

Participants: A total of 110 patients presenting with primary acquired attic cholesteatoma were enrolled in the study. Patients undergoing revision surgery or a canal wall down procedure, as well as patients with residual disease were excluded from the study.
Main outcome measures: During follow-up recurrence was assessed and classified into normal, self-cleaning retraction pockets or recurrent cholesteatoma requiring revision surgery.
Results: We observed during follow-up statistically significant decrease (p=0.036) in the occurrence of retraction pockets and recurrence in patients operated by the transcanal endoscopic approach (n=55, 11% re-retraction, 9% recurrence) compared to those who underwent a canal wall up procedure (n=55, 16% re-retraction, 22% recurrence). However, the multivariate model did not demonstrate statistically significant predictors regarding the outcome. Moreover, the preservation or direct reconstruction of the ossicular chain had a beneficial effect on the outcome. We observed 11% re-retraction and 9% recurrence in cases with preserved or reconstructed ossicular chain versus 18% re-retraction and 24% recurrence (p=0.011) in cases of nonpreserved or non-reconstructed ossicular chain. A score was established according to the intraoperative mucosal damage and correlated to the occurrence of recurrence (p=0.02). The risk of recurrence increased by 23.6% (95% CI: 3.22-48.1) with each additional mucosal damage site.
Conclusion: Transcanal endoscopic approaches that preserve the mastoid may play an important role in preventing recurrence and underscores the importance of the mucosa and mastoid air cells on middle ear homeostasis.

Introduction

Primary acquired cholesteatoma arises most frequently in the epitympanum. Its pathogenesis is still a matter of debate among the scientific community. However, no single hypothesis explains all pathophysiological properties of the disease [1]. The

primordial factor implicated in the occurrence of an attic retraction pocket is considered altered ventilation to the attic and the antrum. Negative attic gas pressures arise as a consequence of blocked aeration routes and resorption of trapped middle ear and mastoid gas. This process of dysventilation leads eventually to the development of a pars flaccida retraction pocket [2]. Moreover, attic dysventilation compromises the gas exchange to the mastoid, impairing its physiologic pressure buffer function. The deeper the retraction pocket grows; the more retention of epithelial debris is observed and finally a cholesteatoma develops. With ongoing growth of the cholesteatoma, the osteoclastic inflammation leads to bone erosion and, if not treated, serious complications such as ossicular chain destruction, facial nerve palsy and erosion and invasion of the skull base and the labyrinth may occur [2].

The surgical treatment of attic cholesteatoma is challenging and the optimal strategy still a matter of debate. The complete removal of cholesteatoma is the primordial goal of the surgical procedures, hence the preservation of middle ear anatomy and physiology is important to restore a normal middle ear function. Several factors influence the homeostasis of middle ear gas exchange. The most important are the function of the Eustachian tube and the pressure buffer mechanism by the middle ear and the mastoid volumes [3,4]. The ventilation of the epitympanum and the mastoid antrum occurs through the tympanic isthmus located between the cochleariform process, the tendon of the tensor tympani muscle and the long process of the incus [5]. This is especially true in cases with a complete tensor fold [6].

Any surgical procedure will unavoidably modify the anatomical and physiological situation of the middle ear and the mastoid. During transmastoid approaches healthy mastoid air cells and a variable degree of middle ear bone and mucosa need to be removed in order to access pathology. Minimal-invasive, transcanal approaches preserve the mastoid air cells and mucosa and therefore their buffer function for gas exchange. In contrast,

mastoidectomy removes most of the mucosal surface, leading to an empty hole in the bone bear of its functional properties. Moreover, the use of transcanal endoscopic exploration of the middle ear allows recognition and immediate treatment of blocked ventilation routes [2].

We aim to investigate the factors associated with recurrent disease following surgery for primary acquired attic cholesteatoma. We hypothesize that minimal invasive, mucosal sparing operation techniques have beneficial effects on the outcome in terms of recurrence. Moreover, we aim to analyze the impact of restoring the middle ear ventilation as well as the type of middle ear reconstruction on the outcome.

Materials and Methods

All patients with primary acquired attic cholesteatoma undergoing surgical treatment at the department of otolaryngology, head and neck surgery of the University Hospital of Modena, Italy during the past twelve years were reviewed for this study. Patients referred to our institution for recurrent disease or a with a history of former ear surgery were excluded. It is the aim of the present study to investigate the impact of mastoid preservation on cholesteatoma recurrence due to persistent physiopathologic alterations. Therefore, patients showing residual disease, defined as a fragment of cholesteatoma matrix left behind during former surgery, as assessed during follow-up or second look surgery were not eligible for the present study. For the same reason, patients undergoing a canal wall down procedure were not included in the present study.

One hundred and ten patients met the inclusion criteria and were enrolled in the study. Our institutional review board does not require particular approval for retrospective chart reviews. The study has been performed according to the Declaration of Helsinki. We assessed initial diagnosis and extend of the pathology using preoperative otoendoscopy recordings and radiological studies. To assess the intraoperative extension of the

cholesteatoma and the anatomical subsites of mucosa removal, we analyzed the surgical video recordings of all procedures from our database. Two senior surgeons (LP and DM) performed all surgical procedures. Either a transcanal exclusive endoscopic (TEE) approach or a canal wall up (CWU) approach were performed. It is our philosophy to check the middle ear for residual disease using an endoscope also during a CWU approach. To We assessed the exact surgical procedure, extent of the cholesteatoma and the removal of tympanic cavity and/or mastoid cavity mucosa. The reconstruction of the ossicular chain and the type of reconstruction of the epitympanum were recorded as well as the type of cholesteatoma matrix (saccular versus infiltrative).

The follow-up of all patients was performed using otoendoscopy in our outpatient clinic and documented in the patient charts. We assessed and classified the postoperative results according to the appearance of the epitympanum into: normal attic appearance; a self-cleaning retraction pocket or a non-self-cleaning retraction pocket defined as recurrent disease requiring prompt revision surgery.

The surgical procedures were

Statistical analysis

The tabularized values were analyzed using Graphpad Prism®. Descriptive statistics were performed for the whole cohort. To analyze the impact of the assessed factors we formed two groups regarding the outcome of the surgery. The effect of the variables on the outcome was measured using unpaired t-tests for continuous variables and Chi-Squared test for categorical variables. Two-tailed p-values were calculated and statistical significance set at alpha<0.05. A univariate logistic regression test was performed to analyze the risk ratio and predictive value of the mucosal damage score. To assess the preoperative disease burden, we compared the disease extension between the surgical approaches using Chi-Squared test. Finally, a multivariate linear Cox regression model

was calculated. Due to the limited number of events (re-retraction or recurrence), the multivariate analysis was restricted to three predictors.

Mucosa damage score

To evaluate the degree of mucosa removal we created a score that classifies surgical alteration of middle ear and mastoid anatomy. In addition to disease extension, this score also includes all mucosa removed for access purposes and summarizes therefore all postoperative surgical alterations to the system. The score allocates according to the estimated mucosa surface: 3 points for mastoidectomy, 2 points for ossicular chain removal and 1 point for mucosa removal from each anatomical subsite of the tympanic cavity (5 points in total for epitympanum, mesotympanum, retrotympanum, hypotympanum and protympanum). All points were then added to a score from 0 (ossicular chain and total mucosa preservation) to 10 (ossicular chain removal and total removal of the mastoid and middle ear mucosa).

Results

A total of 110 cases were analyzed. The mean age at the date of the operation was 37.1 years with a range of 8 to 78 years. The distribution between the TEE approach and the classical CWU procedure was even with 55 patients per group. A detailed description regarding the whole cohort is summarized in Table 1. The cholesteatoma presented in 61.8% of the cases as an infiltrative matrix. The complete eradication of the cholesteatoma matrix required removal of the ossicular chain in 82 cases (74.5%). Thirty-seven patients underwent ossiculoplasty directly during the first operation. Accordingly, we observed a preserved or reconstructed ossicular chain in 65 cases (59.1%). The scutum was reconstructed with cartilage in 47 cases (42.7%), the rest of the patients underwent reconstruction with temporalis muscle fascia only.

After a mean follow up of 29.7 months we observed a physiologic postoperative attic in 78 cases (70.9%), an attic retraction pocket in 15 cases (13.6%) and evident recurrence requiring a second surgical intervention in 17 cases (15.5%). The details and distribution of the analyzed variables regarding the outcome are summarized in table 1.

The extension of the cholesteatoma was assessed and compared between the two surgical groups TEE versus CWU. The results are summarized in table 2. We observed similar disease extension except for the mastoid involvement on preoperative computed tomography (3 TEE vs. 19 CWU, p=0002).

To determine the impact of the different variables on the outcome we compared the normal attic group to both groups showing recurrent pathology in the attic. These results are shown in table 3 and the incidence of recurrence over time is summarized in figure 1. We observed lower rates of recurrent pathology in patients operated by the TEE (11% re-retraction, 9% recurrence) compared to those who underwent a CWU procedure (16% re-retraction, 22% recurrence). The statistical analysis revealed these findings to be statistically significant (p=0.036) with an odds ratio of 0.405. Moreover, the preservation or direct reconstruction of the ossicular chain had statistically significant beneficial effect on the outcome. We observed 11% re-retraction and 9% recurrence in cases with preserved or reconstructed ossicular chain versus 18% re-retraction and 24% recurrence (p=0.011) with an odds ratio of 0.405. The other variables had no statistical significance.

However, the multivariate linear Cox regression model (overall model significance: Prob > chi2 = 0.1737) did not demonstrate statistically significant predictors regarding the outcome, which was re-retraction or recurrent cholesteatoma (hazard ratio of 0.743 (95% CI: 0.334 - 1.651), p=0.466). This data is summarized in table 4.

The proposed mucosa damage score showed increasing values with the appearance of a recurrence. We observed a mean value of 4.26 for patients with normal attic at last follow up. Patients with a recurrent retraction pocket at last follow up had a mean value of 5.40

and patients with recurrence requiring prompt surgical intervention had a value of 5.76. Using the mucosal damage score as single exposure variable, our results show a statistically significant correlation of the score and the occurrence of recurrence (p=0.02), with an odds ratio of 1.236. The risk of recurrence increases of 23.6% (95% CI: 3.22-48.1%) with each additional mucosal damage site.

Discussion

This study investigates the factors associated with recurrent disease following surgery for primary acquired attic cholesteatoma. We observed statistically significant decrease in re-retraction and recurrence rates in patients operated by the TEE approach (9%) compared to those who underwent a CWU procedure (21%) with an odds ration of 0.405 in favor of TEE (p=0.036). However, the multivariate model did not demonstrate statistically significant predictors regarding the outcome (p=0.466). The hazard ratio of 0.743 suggested an effect, however much greater power may be needed to achieve significance. Moreover, the preservation or direct reconstruction of the ossicular chain had a statistically significant beneficial effect on the outcome in the univariate analysis. We observed 11% re-retraction and 9% recurrence in cases with preserved or reconstructed ossicular chain versus 18% re-retraction and 24% recurrence in patients with removed ossicular chain (p=0.011). A novel score was established according to the intraoperative mucosal damage and correlated to the occurrence of recurrence (p=0.02). The risk of recurrence increased by 23.6% (95% CI: 3.22-48.1%) with each additional mucosal damage site. Therefore we suggest a protective function of the mastoid volume and middle ear mucosa preservation to recurrent attic dysventilation and emphasize on the importance of restoring physiologic ventilation patterns during the operation.

The literature presumes the mastoid air cell system to have a pressure buffer function, which is proportional to its volume [3,4]. The surface of the mastoid mucosa is responsible

for gas exchange and maintaining gas pressure balance, which is essential for normal middle ear function [7,8]. From an anatomo-physiological point of view, the middle ear cleft is divided into two separate parts, which are interconnected by the tympanic isthmus. The mesotympanic space is the anteroinferior portion of the middle ear, covered by a pseudostratified epithelium with numerous mucous and ciliated cells. This part is interconnected to the Eustachian tube and is primarily responsible for mucociliary clearance. The second part is represented by the epitympanum, antrum and mastoid spaces in the posterosuperior portion. This area is covered by a richly vascularized monocellular epithelium, without ciliated or mucous cells allowing for gas exchange along pressure gradients. The morphological relationship between the vessels and the mucosal cells supports the gas exchange function theory based on experimental evidence [7,8].
Any surgical procedure alters the anatomical and physiological state of the middle ear, as damage to the mucosa and the bony frame leads to a variable degree of scar tissue. The transcanal access however, offers the surgeon the possibility to preserve the mastoid air cell system and therefore its function. Moreover, healthy middle ear mucosa is preserved as much as possible, as there is no need to remove bone or mucosa for access purposes. It has previously been shown, that the transcanal technique in limited disease has similar recurrence rates as a CWU approach [9]. However, the authors concluded that their results are mainly due to the limited extension of the disease addressed by a transcanal technique. The main condition to achieve reasonable disease eradication in more extended disease is the visibility of the surgical field. This issue is very well addressed by the use of endoscopes inside the middle ear cleft.
Our data represents a very homogeneous cohort. We exclusively analyzed cases with complete disease eradication as assessed during clinical and radiological follow-up and second look surgery. Disease persistence due to incomplete removal of the cholesteatoma matrix does not represent a recurrence of the pathophysiological phenomena leading to

re-retraction of the attic, but rather a failure of the primary surgery. Moreover, the observed intraoperative disease extension is similar in the TEE and the CWU groups, except for mastoid involvement (table 2). Of course, the involvement of the mastoid by cholesteatoma is the main limitation for the TEE technique and a source of confounding for the present study question. In any case, disease eradication has absolute priority in cholesteatoma surgery and mastoidectomy should be performed whenever necessary. Effectively, the effect of TEE on recurrence rates was diminished using a multivariate regression model controlling for mastoid and middle ear involvement. The multivariate model did not demonstrate statistically significant predictors regarding the outcome. Possibly, the attenuation of statistical significance is also due to the limited sample size and the relative rarity of the incidence of recurrent retraction pockets or recurrent cholesteatoma. Although we aimed to minimize every source of bias, this issue remains along with its retrospective design, the main limitation of the present study. As in any retrospective study, sources of bias are present as compared to randomized trials.

A systematic review by Kerckhoffs et al. described recently recurrence rates of 16.7–61.0% for the CWU procedure and 0–13.2% for CWD procedures [10]. Although the size of our cohort is only limited, we observed similar recidivism rates for the CWU (21%), but present significant reduced rates for the TEE approach (9%). Similar favorable results on patients with attic cholesteatoma were published in 2013 [11]. However, a large review article including 86 publications by Kuo et al. concluded that the pros and cons of each technique have to be carefully weighted and the decision of the optimal surgical treatment tailored to the individual situation [12]. The preservation of healthy mucosa is an important consideration in the inside-out technique described by Roth et al., where the size of the access is chosen in function of the extend of the disease [13]. Moreover, a recent histopathological analysis suggested the feasibility of tissue preservation in cholesteatoma surgery [14].

Preservation of the mastoid air cell system by using a TEE approach might result in improved outcomes in patients with acquired cholesteatoma of the attic. This was supported by our univariate, but not multivariate analysis. Restoring a physiologic ventilation pattern and causing only minimal damage to healthy mucosa is a key advantage of the transcanal approach. These considerations are supported by the observations of Tanabe et al. suggesting an improved postoperative aeration of the mastoid by preserving the epitympanic mucosa [15]. In the same line Ahn et al. identified the mastoid involvement to be a prognostic factor for recurrence in pediatric cholesteatoma [16].

Middle ear surgery causes postoperative inflammation. The investigation of the mucosal response during inflammatory diseases showed that the inflammatory process reduces the distance from the blood vessels to the mucosal surface [17]. This observation suggests that gas exchange is more effective and faster during an inflammatory process and may be protective by compensating the increase of negative pressure during inflammatory diseases. In cases of abundant mucosal removal and scarring of the middle ear this important defensive mechanism is lacking, resulting in dysventilation and re-retraction of the neotympanum. In fact, we found a statistically significant correlation of the suggested mucosa damage score to the occurrence of recurrent attic disease. In consequence we believe, that the surgical treatment of cholesteatoma should be tailored to the extension of the disease. A minimal-invasive surgical treatment should be attempted when possible. The preservation of physiological middle ear and mastoid air cell system functions appear to be beneficial for the outcome. Of course, the priority of any surgical intervention in cholesteatoma surgery is the complete eradication of the disease. Thus, in cases of extended disease, requiring the removal of the whole middle ear and mastoid mucosa, a canal wall down procedure with reconstruction of the posterior canal wall may be considered rather than a CWU. Especially in patients with no or minimal mastoid

pneumatization, the complete removal of the epitympanum and the mastoid air cell system to create an open cavity requires no functional postoperative ventilation pathways.

We investigated the impact of removing and reconstructing the ossicular chain on the outcome. In the investigated cohort we observed ossicular chain preservation or reconstruction in 59.1% of the cases. We observed less recurrence in cases with ossicular chain preservation or reconstruction during the first operation (n=13/65, 20%) when compared to cases with ossicular chain removal (n=19/45, 42%) (p=0.011). In our opinion the preserved or reconstructed ossicular chain may serve as a scaffold for the attic reconstruction, especially during the postoperative inflammatory phase, thus improving ventilation. These results however may be subject to a selection bias, since ossicular chain reconstruction in severely diseased ears may not be attempted at the first operation but rather during second look surgery. Although complete disease eradication and restoration of physiologic middle ear function is the main goal in the surgical treatment of cholesteatoma, the outcome regarding the hearing is important for the patient. Our study does not report any hearing results, which represents a major limitation.

The type of reconstruction of the scutum did not affect the outcome. One could expect that a thick cartilage covering the attic may prevent the appearance of a recurrent retraction pocket. This finding suggests, that negative postoperative pressures inside the middle ear may overcome any kind of reconstruction. This is especially true in patients with a pneumatized mastoid. In consequence, the surgeon would be well advised to restore physiological ventilation.

Conclusions

The transcanal exclusive endoscopic approach may play an important role in preventing recurrence by minimizing changes to middle ear and mastoid anatomy. Our observations

underscore the importance of the mucosa and mastoid air cells on middle ear homeostasis.

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	Whole Cohort	Normal Attic	Retraction	Recurrence
Number	110	78	15	17
Age +/- SD (years)	37.1 +/- 19.5	39.1 +/- 18.4	33.7 +/- 18.5	31.1 +/- 21.9
Follow-up +/- SD (months)	29.7 +/- 22.1	29.7 +/- 21.9	24.2 +/- 22.3	34.4 +/- 23.1
Left side	56 (50.9%)	36	9	11
Transcanal approach	55 (50%)	44	6	5
Canal wall up approach	55 (50%)	34	9	12
Sacculated matrix	42 (38.2%)	33	4	5
Infiltrative matrix	68 (61.8%)	45	11	12
Ossicular chain preservation or reconstruction	65 (59.1%)	52	7	6
Scutum reconstruction with cartilage	47 (42.7%)	33	6	8
Mean mucosa damage score +/- SD	4.65 +/- 2.81	4.26 +/- 2.75	5.40 +/- 2.56	5.77 +/- 3.01

Table 1: General patients' characteristics. The data is shown for the whole cohort and grouped by outcome.

Features		TEE (n=55)	CWU (n=55)	p-value
Attic extension	Limited	25	19	0.331
	Extended	30	36	
Attic and Antrum extension	Limited	19	24	0.435
	Extended	36	31	
Involvement of middle ear	None	44	43	>0.999
	Extended	11	12	
Mastoid involvement	None	52	36	0.0002
	Yes	3	19	
Ossicular chain erosion	None	20	20	>0.999
	Yes	35	35	

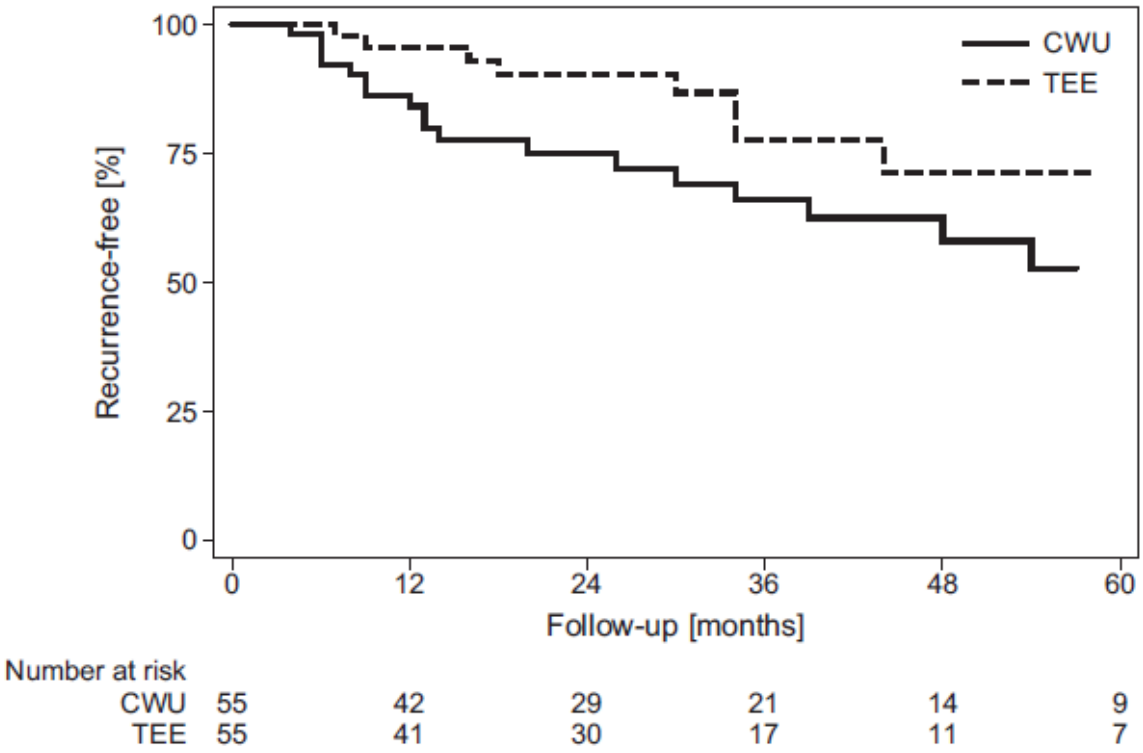
Table 2: Comparison of cholesteatoma extension by surgical approach. We observed similar disease extension in both surgical groups. The only statistically significant difference was mastoid extension. TEE: transcanal exclusive endoscopic approach, CWU: canal wall up procedure. Univariate p-values were calculated by Chi-square tests.

Features		Normal attic	Retraction/ Recurrence	Odds ratio	p-value
Approach	TEE	44	11	0.405 (0.176 - 0.916)	**0.036**
	CWU	34	21		
Ossicular chain	Preserved or reconstructed	52	13	0.342 (0.154 - 0.777)	**0.011**
	Removed	26	19		
Matrix type	Sacculated	33	9	0.534 (0.229 - 1.263)	0.167
	Infiltrative	45	23		
Scutum reconstruction	Fascia	45	18	1.061 (0.456 - 2.365)	0.891
	Cartilage	33	14		
Follow-up	Months	29.71	29.63	-	0.988

Table 3: Univariate outcome analysis. Statistically significant beneficial effects were observed for the exclusive endoscopic approach as well as for the ossicular chain preservation or reconstruction. TEE: transcanal exclusive endoscopic approach, CWU: canal wall up procedure, p-values were calculated by Chi-square tests.

Variable	Hazard ratio	95% confidence interval	p-value
TEE approach	0.743	0.334 - 1.651	0.466
Middle ear extension	1.471	0.596 - 3.635	0.403
Mastoid involvement	1.815	0.761 - 4.329	0.179

Table 4: Multivariate outcome analysis. The multivariate Cox regression model (overall model significance: Prob > chi2 = 0.1737) shows an attenuation of the effect of the transcanal exclusive endoscopic approach (TEE) on the outcome (normal attic versus recurrent disease). It did not demonstrate statistically significant predictors regarding the outcome.



Number at risk

CWU	55	42	29	21	14	9
TEE	55	41	30	17	11	7

FIG. 1. Kaplan–Meier estimates for recurrence during follow-up period. CWU indicates canal wall up; TEE, transcanal exclusive endoscopy.